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The technical objectives of this infrastructure enhancement project are to establish a population-based biological specimen and data bank on 225 women with invasive breast cancer, aged 35 and under. This new resource will be available to multiple investigators to identify and determine the frequency of inherited gene alterations in p53, BRCA1 and additional inherited breast cancer susceptibility genes, and studies of gene-environmental interactions. Our cases will help refine estimates of germinal mutation frequency among young patients who have no family history of breast cancer. Work is on schedule so that 225 young cases will be ascertained over 36 months through the tumor incidence registries in Connecticut, Massachusetts and 7 regions in California. Demographic, epidemiologic and family history data are being collected, paraffin-fixed tumor tissue retrieved, and fresh blood specimens will be processed to produce genomic DNA, a plasma specimen, and viably frozen cells. A computerized file of the epidemiologic data and specimen data will be made accessible to all researchers via the Internet.

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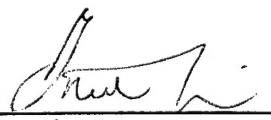

10/21/96

PI - Signature Date

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INTRODUCTION

An estimated 180,000 women in the US are diagnosed with invasive breast cancer each year (1). The lifetime risk of developing breast cancer is 1 in 9 by age 80 (2). Breast cancer accounts for 30 percent of incident cancer among American women, and 18 percent of cancer deaths. Age-adjusted breast cancer incidence rates have risen from 85/100,000 to 112/100,000 during the period 1980-87 (3). Part of the increase is likely to be the effect of greater use of mammography which has detected breast cancers at earlier stages and at smaller sizes. In contrast, breast cancer mortality rates have declined slightly during these intervals, reflecting steady improvements in survival rates after therapy (1).

Many studies of breast cancers in families have consistently shown that a positive family history is a potent risk factor for breast cancer (4-11). Data indicate that familial disease tends to arise at younger ages, often bilaterally in both breasts. In many families with multiple affected relatives, the pattern of involvement is consistent with autosomal dominant inheritance with high penetrance. In the Cancer and Steroid Hormone (CASH) Study, women who had one affected first-degree relative had a relative risk (RR)=2.3 when compared to women with negative family histories (8). However, RR=14 for those with both an affected mother and sister. Data of the Nurses' Health Study also demonstrated excess risk, but at a somewhat lower magnitude (7). Dupont and Page found that family history further increases the risk of breast cancer in women with atypical hyperplasia on breast biopsy (6).

Genetic alterations underlie the process of the transformation of a normal cell into a cancer cell. Among the estimated 100,000 genes in the human genome, only a small fraction seems to be critical in cancer development. Mutations in these genes can occur as a consequence of exposure to environmental carcinogens, spontaneous mutations, or inheritance of the trait. Some inherited cancer genes markedly increase the likelihood of cancer development in carriers to nearly 100 percent (13). Hereditary breast cancer is estimated to account for approximately 7-8 percent of all breast cancers in the US, though the range of estimates spans 3-19 percent (4, 11-13). Recent data have identified 4 inherited single-gene defects (ATM, BRCA1, BRCA2 and p53) that predispose to breast cancer (14-17).

To date, studies of early-onset breast cancer patients were critical to the identification of 2 important heritable breast cancer susceptibility genes, BRCA1 and BRCA2 (15, 18). These genes account for an estimated 70 percent of hereditary breast cancers. The genes for the remaining 30 percent are also likely to be found through additional studies of early-onset cases. We are collecting risk factor data, a blood sample and paraffin blocks on women who were diagnosed with invasive breast cancer under age 35 in Massachusetts, Connecticut and seven regions of California. With the development of an anonymous specimen bank of incident breast cancers, we will be providing the infrastructure for the identification of studies of inherited breast cancer susceptibility genes, and their interactions with hormonal and environmental risk factors.

BODY

The purpose of our project is to develop a biological specimen bank and epidemiological database of 225 early-onset invasive breast cancer cases (age 34 and under). To achieve this purpose, we will be enrolling all eligible cases in the population-based cancer incidence registries in Connecticut, Massachusetts and 6 regions of California (Santa Clara region, Central Valley, Sacramento, Inland Empire, San Diego, Bay Area and Orange regions). Based on available data, approximately one-third of breast cancer cases under age 33 are carriers of an inherited gene: estimated carrier rates are 36% at ages 20-29; 29% at age 30; 28% at age 31; and 27% at age 32 years. This project will establish a national resource which can be used to: define the frequency and patterns of constitutional alterations in the BRCA1/2 genes and other predisposing genes not

yet identified in young breast cancer patients; define the clinical characteristics and risk factor profiles of anonymous breast cancer patients with constitutional mutations in a cancer susceptibility gene; examine possible interactions between environmental exposures and genetic susceptibility to breast cancer; and, assess loss of heterozygosity and other acquired genetic changes in tumors of the breast which may occur in gene carriers.

The cases are generated from a population base of 21 million (8% of entire US population) that is of special interest to breast cancer researchers. Age-adjusted cancer mortality rates for 1985-89 show that Massachusetts ranks 6th highest nationwide, and Connecticut ranks 13th (1,19). Both states are in the high breast cancer-mortality belt that spans the Middle Atlantic and New England regions. California, the most populous state in the nation, has substantial minority populations, including Asian-Americans (9.9%), Hispanic-Americans (20.9%), and Black-Americans (6.1%) in the study regions. The racial composition of Massachusetts is 88% Whites, 5% Hispanics, 5% Blacks, 2% Asians and 0.6% others. In Connecticut, there are 83% Whites, 8% Blacks, 7% Hispanics and 2% Asians and 0.1% others.

In order to create the resource, we are proceeding to accomplish the following: identify all 410 incident invasive breast cancer cases, ages 34 and under in an 36-month period, using available rapid case ascertainment systems for the population covered by the cancer incidence registries of the State of Connecticut, Commonwealth of Massachusetts, and 6 regions in California; with permission of the treating physician and the patient, complete a questionnaire, collect a breast cancer paraffin block, and draw 50 mls of peripheral blood for at least 225 subjects; use the blood sample to establish a lymphoblastoid line, produce genomic DNA, a plasma specimen, and store viably frozen cells along with paraffin blocks in laboratories of the Principal Investigator (PI) and co-PIs in California and Massachusetts; identify families informative for linkage and collect available paraffin blocks and blood samples from relatives for molecular analyses; and place all questionnaire and specimen summary data into a computerized file that can be accessed by electronic mail, and publicize the resource.

The methods of case ascertainment are designed to achieve the highest possible participation rate, defined as completion of the questionnaire and collection of the blood specimen and paraffin block from study subjects. Mechanisms have been established for rapid case ascertainment of all incident cases, ages 34 and under (approximately 410 cases within the initial 36 months of the project); obtaining informed consent from subjects; administering a standardized interview; performing a phlebotomy and processing the specimen (20-27). Rapid case ascertainment systems differ slightly in California, Massachusetts and Connecticut. The approach in each region has been determined by cost considerations and established resources.

In Year 2 of this 4-year project, we have continued to enumerate eligible study subjects through the cancer incidence registries of Connecticut, Massachusetts and seven regions of California. Since 1987, a Rapid Case Ascertainment system in Connecticut has identified over 40,000 cancer cases potentially eligible for the Federally-funded population-based research projects. For these studies, eligible subjects were identified through 35 hospitals that reported to the Connecticut Tumor Registry. In Massachusetts, a similar system is in use based on the Connecticut model. By California law, any cancers diagnosed at any facility in the state must be reported. Established in 1983, CSPOC (Cancer Surveillance Program of Orange County) has developed into a model registry for implementing the 1985 legislation which made cancer a reportable disease throughout California.

California cases are handled through University of California, Irvine (UCI), and Massachusetts and Connecticut cases are through Dana-Farber. Consent to participate in this study is a 2-step process. Initially, the physician of the subject is contacted for permission to inform the patient of the study and request voluntary participation (Appendix 1). With physician consent, the patient is

sent a letter that explains the study, and subsequently telephoned (Appendix 2). After the patient gives verbal consent, a telephone questionnaire will be administered (Appendix 3).

Arrangements are made for collection of 50 ml of peripheral blood by venipuncture at a facility specified by the patient. The participant may choose to either have her blood drawn at her next doctor's appointment or may have a Visiting Nurse come to her home to draw her blood. Signed consent is obtained prior to the blood draw (Appendix 4). The blood sample is sent to the laboratories at UCI and Massachusetts General Hospital (MGH) for processing; the Repository will be at MGH. Based on an estimate of 410 eligible cases to be identified during the 36 months of patient eligibility, data and specimens will be collected on at least 225 subjects. An Outside Advisory Committee of leading scientists will prioritize requests from any breast cancer investigator for biologic specimens.

No laboratory test results on specimens distributed to outside investigators will be released to the participant or her physician because interim laboratory results might be wrong. If the patient feels that it would be too difficult for her not to know the results, she may decide not to give a blood sample and therefore not participate in the study. Every participant will be asked whether she wishes to be notified when a commercial or clinical test for BRCA1 is available from any source. Should a participant decide to have the test performed, her participation in this study will not be affected.

The patient has the option of designating one tube of blood for future studies by the PIs. These tubes of blood will not become part of the resource. If, in the future, specific findings are documented in the participant from this tube of blood, the participant will be offered the opportunity to learn the results of the research. Disclosure of results will occur in a study separate from this one; clinical intervention, including genetic counseling, will be available.

To ensure confidentiality, a number will be assigned to each subject. Labels with these numbers are placed on all blood tubes and tumor tissues, and assigned to the questionnaire. The receiving laboratory at MGH receives these samples with all personal identifiers stripped. All subject records will be stored in locked file cabinets and all computer files will be kept locked with restricted access passwords. The list of names and matching code numbers will be stored separately from the other study information and will be available only to the study supervisors. All specimens sent to outside investigators will be stripped of identifiers. Questionnaire data will be supplied to outside investigators as a pooled sample (i.e. 15 women between the ages of 25 and 30 years). No information that identifies an individual subject will be given to third parties, including family members, unless that subject has given consent to do so.

Methods have been defined to uniformly collect blood specimens, tumor paraffin-blocks, and questionnaire data from 410 incident invasive breast cancer cases (age 34 and under) ascertained in Years 1 and 2 through the population-based cancer registries for Massachusetts and Connecticut, and 6 participating regions of California. During Year 3 (1997), processing of specimens and establishment of a tissue repository and epidemiologic database for at least 225 cases will be nearly completed. At Year 4, the database will be kept on-line for e-mail accession, and specimens will be distributed worldwide to investigators who have applied to use specimens from the resource. The combined prior experience and preliminary data collected by the PI and co-PIs assures that the project will be completed as described.

As of September 30, 1996, 309 patients have been identified as eligible for the study and are in various stages of entry and participation in the study. Participation rate is very high, and only isolated refusals have been enumerated. To date, 92 patients from Massachusetts, 71 from Connecticut and 146 from California are eligible. Forty-seven eligible patients are not participating, either because the physician refused to grant us permission to contact the patient or because the patient herself refused participation. Thus far, 150 patients have completed the

questionnaire and 101 have given a blood sample. The blood samples that have been collected have been processed by the receiving lab and have been put into the Repository. Over 85% of the samples received have successfully generated cell lines. Additionally, 33 paraffin blocks have been received for the Repository. Paraffin blocks are becoming increasingly difficult to collect. Hospitals are reluctant to release them for reasons of their own research and medical-legal concerns. Also, they are charging for paraffin blocks and slides (Appendix 5). The PI will consider options with the Project Officer.

Initially, patient identification and accrual proceeded more slowly than we anticipated due to resistance of many Institutional Review Boards to DOD language requirements in consent forms. Our experience has been that Institutional Review Boards take months before our protocol can be approved. A great deal of investigator time has been consumed in negotiations to modify consent forms to be acceptable to both DOD and individual IRBs. Several hospitals have been dropped where no agreement was reached. In this matter, our Project Officer (Brian Martin) and Human Use Review Specialist (Catherine Smith) have been most helpful. Even Rapid Case Ascertainment systems can have a lag time of six months before a case is reported. Some of the patients are accrued through hospital tumor registries, and months elapse between time of the submission of the protocol and the enrollment of the patient. For the most part, these issues have been addressed and patient identification is continuing without much delay. However, the lag time between the diagnosis of cancer and the reporting to the tumor registry by the hospital, particularly in Massachusetts, continues to be problematic. Massachusetts is instituting a new reporting system which is not yet operational and delays the reporting of eligible patients to the Investigators. Over the last year, we have kept pace with our timeline, and we will use the next year to catch-up with the deficit from Year 1 due to IRB issues.

CONCLUSION

The study should be successfully carried out as proposed. However, funding at 50% of originally requested funds has slowed the process of case accrual. In addition, IRBs are generally unfamiliar with DOD informed consent requirements. Lengthy time-consuming negotiations have been needed before the protocol was approved. Each hospital has required different modifications, and some are reluctant to release tumor blocks or are assessing a charge for handling. Despite these obstacles, we expect to have the specimen resource available for use according to the schedule proposed in the application.

The implications of the project are that our resource will be useful in determining the population-based frequency of BRCA1 and BRCA 2 and other susceptibility genes in early-onset cases, as well as determining environmental risk factors common to our patient pool. Also, the materials will be useful in cloning and defining the phenotypic features of BRCA3 and additional genes.

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APPENDIX 1:

Physician Letter

«DATA Macintosh HD:DOD/Breast Cancer:mailings:md.address»

October 21, 1996

«mdfname» «mdlname», MD
«hospname»
«add1»
«add2»
«add3»

Dear Dr. «mdlname»:

We have begun a research survey study funded by the US Army Breast Cancer Research Program to identify and study inherited mutations in breast cancer susceptibility genes in young patients. This letter is written to ask for your consent to contact one of your patients, «patname», who was diagnosed with breast cancer before age 35 years. She came to our attention either through your hospital or state tumor registry.

You may be aware that the BRCA1 gene was recently cloned, making this study timely. Data show that as many as 5-10% of women with breast cancer carry alterations in genes that confer increased susceptibility to breast cancer. However, the frequency of inherited susceptibility to breast cancer is approximately 25% in women who develop breast cancer before age 35.

We would like to obtain a blood specimen from «patname» as part of a tissue bank to study breast cancer susceptibility genes. We ask that either you ask the patient for permission or give us approval to contact her directly. In either case, the purpose of this study will be explained to the patient in writing. We will ask the patient to provide us with a blood specimen (up to 50 ml) and to complete a questionnaire including information about her breast cancer risk factors and cancer history. We do not intend to report individual genetic information back to you or the patients as part of this exploratory study. However, your patient may designate that some of her blood can be stored for possible future study in which DNA results will be disclosed; this future study, if undertaken, will be conducted under a separate protocol to be approved by our IRB.

Participation by you and your patient in this study is entirely voluntary. We would not expect that participation of your patient in this study would alter your relationship with her in any way.

We would appreciate your filling in the attached form and returning it to us by FAX or mail at your earliest convenience. An envelope is included to assist in returning this form. Please do not hesitate to call; we would be delighted to answer any questions that you may have.

Sincerely,

Frederick P. Li, MD
Principal Investigator
(617)632-3158

Elizabeth Claus, MD, Ph.D
Co-Principal Investigator
(203)785-2838

EARLY BREAST CANCER STUDY

The following patient's name has been supplied to us by the «hospname» as treated by you. We would like the patient's current address, telephone number and your permission to contact by mail or telephone.

HOSPITAL ID	«hospid»
PATIENT NAME	«PATNAME»
AGE AT DIAGNOSIS	«age@dx»
DATE OF DX	«date dx»

PLEASE FILL OUT THE ITEMS IN THE SHADED AREA AND FAX THIS FORM TO:

EARLY BREAST CANCER STUDY
(617)632-3161

Attn: Frederick P. Li, MD

NAME: «patname»

ADDRESS: _____

_____

_____

TELEPHONE: (_____) _____

CONTACT FOR CONSENT:

( ) **You have my permission to contact this patient**

( ) **I've already contacted patient, she's expecting your call**

( ) **Do not contact this patient**

COMMENTS/SPECIAL INSTRUCTIONS: _____

_____

_____

_____

Your signature

«mdfname» «mdlname», MD

If you prefer, mail the form to us at the following address:

Frederick P. Li, MD
Attn: Early Breast Cancer Study
44 Binney Street, Mayer 3A.31
Boston, MA 02115

APPENDIX 2:

Patient Letter

«DATA Macintosh HD:DOD/Breast Cancer:mailings:patient.address»

October 21, 1996

«fname» «lname»
«add1»
«add2»

Dear Ms. «lname»:

We would like to ask for your help with a new research study to identify the causes of breast cancer in young women. Your physician, Dr. «mdlname», has given us permission to contact you.

It has been estimated that 25% of women who develop breast cancer before age 35 may have been born with an altered gene that increases the chances of developing breast cancer. Susceptible women may have no prior family history of breast cancer. This study has been designed to establish a tissue bank for research to learn how often young women with breast cancer actually were born with an altered gene that increases chances of developing breast cancer. The long-term goal of the project is to be able to answer such questions as, "who is at increased risk for breast cancer?" and "can we learn to detect disease earlier when intervention is more helpful?" Understanding the inheritance of breast cancer risk may be important for the family members of women with breast cancer. The BRCA1 (BReast CAncer 1) gene was identified recently and has received a lot of attention in the news media.

We are writing to invite you to participate in this research study. We are asking you to donate a blood sample and answer a standard questionnaire. There will be approximately 250 women diagnosed with breast cancer at age 34 or younger in the study. This work will take several years. Although we hope and expect that information will be learned that may be helpful to women who have developed breast cancer, this work may not directly benefit you. In this study, we will not be releasing any laboratory results of our analysis to you or your doctor. Participation in this study will not alter your current care or follow-up in any way and you will continue to be cared for by your own doctors. Your participation will, however, help us learn more about the causes of breast cancer, particularly in younger women.

If you are willing to participate in this research study, we ask that you complete and return the enclosed response form. We will then call you to arrange for an opportunity to go over the questionnaire with you and to obtain a blood sample (50 ml or less than 4 tablespoons). The blood drawing can be done either during your next visit with your doctor or through other arrangements. All information obtained will be kept strictly confidential.

Thank you very much for considering participation in this important research project. Please take a moment to answer the response form and return it to us in the enclosed envelope.

Sincerely,

Frederick P. Li, MD

Elizabeth Claus, MD, Ph.D

RESPONSE FORM

I, «fname» «lname», patient of Dr. «mdlname»,

☐ am not interested in participating in this project.

☐ am interested in learning more about the Early Breast Cancer Study.

Signed: _____
«fname» «lname» Date

The best way to reach me is:

☐ at home

phone # _____ - _____ - _____

hours: _____

☐ at work

phone # _____ - _____ - _____

hours: _____

☐ other _____
(please specify)

address: _____

_____

_____

phone # _____ - _____ - _____

APPENDIX 3:

Questionnaire

APPENDIX D

94-161

ID#: _____

Interviewer ID: _____

Time Interview Began: _____ am/pm

Time Interview Ended: _____ am/pm

Date of Interview: _____

Outcome Code: _____

Reference Date: _____

Early Breast Cancer Study

Hello, my name is (YOUR NAME). May I please speak with (RESPONDENT)? I'm calling on behalf of (The Dana-Farber Cancer Institute/Yale University School of Medicine/The University of California at Irvine Medical School).

A. Recently, we spoke and wrote to you about our study of women with breast tumors, and asked you to participate. We would like to ask you some questions now about your health and your family's health. Your answers to these questions will help us in our goal to understand some of the causes of cancer. By taking time to answer our questions, you may be helping us improve our ability to prevent or treat the disease in the future.

B. (IF APPOINTMENT LETTER WAS SENT) Did you receive a copy of the consent form with your appointment letter? Have you had a chance to read it? Do you have any questions so far about the consent or the questionnaire? Do you agree to be interviewed?

(IF APPOINTMENT LETTER WAS NOT SENT) I would like to read the introduction and the section regarding the questionnaire from the Study Consent to you. (READ APPROPRIATE SECTIONS FROM THE STUDY CONSENT.) Do you have any questions about the consent or questionnaire? Do you agree to be interviewed?

C. Your cooperation in the survey is entirely voluntary, and all the information collected will be confidential. Neither your name nor any other identifying information will appear in any report of the survey.

D. The interview will take about 20 minutes. We're going to ask about family members and their health, then concentrate on you. First, though, I'd like to begin by asking a few questions about your background.

A. DEMOGRAPHIC INFORMATION

A1. What is your date of birth?

_____/ ___/_____

A2. What is the highest degree or year of school you have completed? (DO NOT READ CATEGORIES)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (PH.D., M.D., J.D.)
[ ] OTHER (SPECIFY: _____)

A3. What is your current living situation or marital status? By that I mean, are you:

[ ] married
[ ] separated
[ ] divorced
[ ] widowed
[ ] living as married
[ ] never married (single)

A4. In what religion were you raised? (DO NOT READ CATEGORIES)

[ ] BAPTIST
[ ] EPISCOPALIAN
[ ] GREEK ORTHODOX
[ ] JEWISH
[ ] LUTHERAN
[ ] METHODIST
[ ] MORMON (LATTER DAY SAINTS)
[ ] PRESBYTERIAN
[ ] PROTESTANT
[ ] ROMAN CATHOLIC
[ ] UNITARIAN
[ ] OTHER (SPECIFY: _____)

A5. Would you describe yourself as white, black, Hispanic, Asian, or other? (IF OTHER, PROBE FOR ETHNIC GROUP OR RACE)

[ ] WHITE
[ ] BLACK
[ ] HISPANIC OR MEXICAN AMERICAN
[ ] ASIAN OR PACIFIC ISLANDER
[ ] NATIVE AMERICAN
[ ] OTHER (SPECIFY: _____)

A6. IF EVER MARRIED: What is the highest degree or year of school that your husband or partner completed? (DO NOT READ CATEGORIES; IF MORE THAN ONE HUSBAND/PARTNER, ASK FOR MOST RECENT)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (PH.D., M.D., J.D.)
[ ] OTHER (SPECIFY: _____)

B. FAMILY HISTORY

Now I have some questions about your immediate blood relatives. By immediate blood relatives I mean your parents and your brothers and sisters.

B1. First, were you adopted?

[ ] Yes (C1)
[ ] No (B2)

B2. Is your mother still living?

[ ] Yes (B3)
[ ] No (B4)

B3. How old is your mother? _____ (B5)

B4. How old was your mother when she died? _____

B5. Did your mother ever have breast cancer or ovary cancer?

[ ] YES, BREAST CANCER, ONE BREAST (B6)
[ ] YES, BREAST CANCER, BOTH BREASTS (B6)
[ ] YES, OVARY CANCER (B6)
[ ] NO (B7)

B6. How old was she when it was first diagnosed? _____ (BREAST)
_____ (OVARY)

B7. Did your mother ever have any other kind of cancer?

[ ] Yes (B8)
[ ] No (B10)

B8. What kind of cancer(s) did she have?	B9. How old was she when it was diagnosed?
a. _____	a. _____
b. _____	b. _____

B10. Is your father still living?

[ ] Yes (B11)
[ ] No (B12)

B11. How old is your father? _____ (B13)

B12. How old was your father when he died? _____

B13. Did your father ever have cancer?

[ ] Yes (B12)
[ ] No (B14)

B14. What kind of cancer(s) did he have?	B15. How old was he when it was diagnosed?
a. _____	a. _____
b. _____	b. _____
c. _____	c. _____

Let's continue with your sisters and brothers, both living and deceased.

B16. Altogether, how many sisters or half sisters have you had? _____ (B17)
[ ] None, or adopted (B26)

		Oldest Sister	2nd Sister	3rd Sister
B17.	Is your (oldest, 2nd, etc.) sister still living?	[ ] Yes (B18) [ ] No (B19)	[ ] Yes (B18) [ ] No (B19)	[ ] Yes (B18) [ ] No (B19)
B18.	How old is she?	_____ (B20)	_____ (B20)	_____ (B20)
B19.	How old was she when she died?	_____	_____	_____
B20.	Is she your full sister, half sister, or an adopted sister ?	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (NEXT SISTER)	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (NEXT SISTER)	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (B26)
B21.	Did she ever have breast cancer or ovary cancer?	[ ] Yes, breast, one [ ] Yes, breast, both [ ] Yes, ovary [ ] No (B23)	[ ] Yes, breast, one [ ] Yes, breast, both [ ] Yes, ovary [ ] No (B23)	[ ] Yes, breast, one [ ] Yes, breast, both [ ] Yes, ovary [ ] No (B23)
B22.	How old was she when it was diagnosed?	a. _____ (BREAST) b. _____ (OVARY)	a. _____ (BREAST) b. _____ (OVARY)	a. ___(BREAST) b. ___(OVARY)
B23.	Did she ever have any other kind of cancer?	[ ] Yes (B24) [ ] No (NEXT SISTER)	[ ] Yes (B24) [ ] No (NEXT SISTER)	[ ] Yes (B24) [ ] No (B26)
B24.	What kind of cancer did she have?	a. _____ b. _____	a. _____ b. _____	a. _____ b. _____
B25.	How old was she when it was diagnosed?	a. _____ b. _____ (NEXT SISTER)	a. _____ b. _____ (NEXT SISTER)	a. _____ b. _____

B34. Are you a twin?
[ ] Yes
[ ] No (B37)

B35. Which brother or sister is your twin?
[ ] Brother #__ (B37)
[ ] Sister #__ (B36)

B36. Are you identical twins?
[ ] Yes
[ ] No
[ ] Don't Know

(IF RESPONDENT HAS NO SIBS, GO TO B38)

B37. Are any of your brothers or sisters twins?
[ ] Yes (Specify:_____)
[ ] No (B39)

B38. Are they identical twins?
[ ] Yes
[ ] No
[ ] Don't Know

Now I have some questions about other relatives. I will begin with your mother's parents and her side of the family.

B39. First, was your mother adopted?
[ ] Yes (B73)
[ ] No
[ ] Don't Know

B40. Is your mother's mother still living?
[ ] Yes (B41)
[ ] No (B42)

B41. How old is your mother's mother? ____

B42. How old was your mother's mother when she died? ____

B43. Did your mother's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No (B45)
[ ] Don't Know (B45)

B44. How old was she when it was first diagnosed?

_____ (Breast)
_____ (Ovary)

B45. Did your mother's mother ever have any other kind of cancer?

[ ] Yes (B46)
[ ] No (B48)
[ ] Don't Know (B48)

B46. What kind of cancer(s) did she have?
a._____
b._____
c._____

B47. How old was she when it was diagnosed?
a._____
b._____
c._____

B48. Is your mother's father still living?

[ ] Yes (B49)
[ ] No (B50)

B49. How old is your mother's father?

_____ (B51)

B50. How old was your mother's father when he died?

_____

B51. Did your mother's father ever have have cancer?

[ ] Yes (B52)
[ ] No (B54)
[ ] Don't Know (B54)

B52. What kind of cancer(s) did he have?

a._____
b._____
c._____

B53. How old was he when it was diagnosed?

a._____
b._____
c._____

Now I will ask you about your mother's brothers and sisters, both living and deceased.

B54. Altogether, how many sisters or half-sisters did your mother ever have? _____ (B55)
[ ] None (B64)

		Oldest Sister	2nd Sister	3rd Sister
B55.	Is her (oldest, 2nd, etc.) sister still living?	[ ] Yes (B56) [ ] No (B57)	[ ] Yes (B56) [ ] No (B57)	[ ] Yes (B56) [ ] No (B57)
B56.	How old is she?	_____ (B58)	_____ (B58)	_____ (B58)
B57.	How old was she when she died?	_____	_____	_____
B58.	Is she your mother's full sister, half sister, or an adopted sister ?	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (NEXT SISTER)	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (NEXT SISTER)	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (B64)
B59.	Did she ever have breast cancer or ovary cancer?	[ ] Yes, breast [ ] Yes, breast both [ ] Yes, ovary [ ] No (B61) [ ] Don't Know (B61)	[ ] Yes, breast [ ] Yes, breast both [ ] Yes, ovary [ ] No (B61) [ ] Don't Know (B61)	[ ] Yes, breast [ ] Yes, breast both [ ] Yes, ovary [ ] No (B61) [ ] Don't Know(B61)
B60.	How old was she when it was diagnosed?	a. _____ (BREAST) b. _____ (OVARY)	a. _____ (BREAST) b. _____ (OVARY)	a. ___ (BREAST) b. ___ (OVARY)
B61.	Did she ever have any other kind of cancer?	[ ] Yes (B62) [ ] No (NEXT SISTER) [ ] Don't Know (NEXT SISTER)	[ ] Yes (B62) [ ] No (NEXT SISTER) [ ] Don't Know (NEXT SISTER)	[ ] Yes (B62) [ ] No (B64) [ ] Don't Know(B65)
B62.	What kind of cancer did she have?	a. _____ b. _____	a. _____ b. _____	a. _____ b. _____
B63.	How old was she when it was diagnosed?	a. _____ b. _____ (NEXT SISTER)	a. _____ b. _____ (NEXT SISTER)	a. _____ b. _____

B64. Altogether, how many brothers or half-brothers did your mother ever have? ___ (B65)
[ ] None (B73)

		Oldest Brother	2nd Brother	3rd Brother
B65.	Is her (oldest, 2nd, etc.) brother still living?	[ ] Yes (B66) [ ] No (B67)	[ ] Yes (B66) [ ] No (B67)	[ ] Yes (B66) [ ] No (B67)
B66.	How old is he?	_____ (B68)	_____ (B68)	_____ (B68)
B67.	How old was he when he died?	_____	_____	_____
B68.	Is he your mother's full brother, a half brother or an adopted brother?	[ ] Full brother [ ] Half brother (mother's side) [ ] Half brother (father's side) [ ] Adopted (NEXT BROTHER)	[ ] Full brother [ ] Half brother (mother's side) [ ] Half brother (father's side) [ ] Adopted (NEXT BROTHER)	[ ] Full brother [ ] Half brother (mother's side) [ ] Half brother (father's side) [ ] Adopted (B72)
B69.	Did he ever have any kind of cancer?	[ ] Yes (B70) [ ] No (NEXT BROTHER) [ ] Don't Know (NEXT BROTHER)	[ ] Yes (B70) [ ] No (NEXT BROTHER) [ ] Don't Know (NEXT BROTHER)	[ ] Yes (B70) [ ] No (B72) [ ] Don't Know(B72)
B70.	What kind of cancer did he have?	a. _____ b. _____	a. _____ b. _____	a. _____ b. _____
B71.	How old was he when it was diagnosed?	a. _____ b. _____ (NEXT BROTHER)	a. _____ b. _____ (NEXT BROTHER)	a. _____ b. _____

B72. Was your mother or her brothers or sisters twins?

[ ] Yes (specify:_____)
[ ] No

Now I have some questions about your father's parents and his side of the family.

B73. First, was your father adopted?
[ ] Yes (C1)
[ ] No
[ ] Don't Know

B74. Is your father's mother still living?
[ ] Yes (B75)
[ ] No (B76)

B75. How old is your father's mother? _____ (B77)

B76. How old was your father's mother when she died? ____

B77. Did your father's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No (B79)
[ ] Don't Know (B79)

B78. How old was she when it was first diagnosed?

_____ (Breast)
_____ (Ovary)

B79. Did your father's mother ever have any other kind of cancer?

[ ] Yes (B80)
[ ] No (B82)
[ ] Don't Know (B82)

B80. What kind of cancer(s) did she have?
a._____
b._____
c._____

B81. How old was she when it was diagnosed?
a._____
b._____
c._____

B82. Is your father's father still living?
[ ] Yes (B83)
[ ] No (B84)

B83. How old is your father's father? _____ (B85)

B84. How old was your father's father when he died? ____

B85. Did your father's father ever have have cancer?
[ ] Yes (B86)
[ ] No (B88)
[ ] Don't Know (B88)

B86. What kind of cancer(s) did he have?
a._____
b._____
c._____

B87. How old was he when it was diagnosed?
a._____
b._____
c._____

Now I will ask you about your father's brothers and sisters, both living and deceased.

B88. Altogether, how many sisters or half-sisters did your father ever have? _____ (B90)
[ ] None (B99)

		Oldest Sister	2nd Sister	3rd Sister
B89.	Is his (oldest, 2nd, etc.) sister still living?	[ ] Yes (B90) [ ] No (B91)	[ ] Yes (B90) [ ] No (B91)	[ ] Yes (B90) [ ] No (B91)
B90.	How old is she?	_____ (B92)	_____ (B92)	_____ (B92)
B91.	How old was she when she died?	_____	_____	_____
B92.	Is she your father's full sister, half sister, or an adopted sister ?	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (NEXT SISTER)	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (NEXT SISTER)	[ ] Full sister [ ] Half sister (mother's side) [ ] Half sister (father's side) [ ] Adopted (B98) (NEXT SISTER)
B93.	Did she ever have breast cancer or ovary cancer?	[ ] Yes, breast [ ] Yes, breast both [ ] Yes, ovary [ ] No (B95) [ ] Don't Know (B95)	[ ] Yes, breast [ ] Yes, breast both [ ] Yes, ovary [ ] No (B95) [ ] Don't Know (B95)	[ ] Yes, breast [ ] Yes, breast both [ ] Yes, ovary [ ] No (B95) [ ] Don't Know(B95)
B94.	How old was she when it was diagnosed?	a. _____ (BREAST) b. _____ (OVARY)	a. _____ (BREAST) b. _____ (OVARY)	a. ___ (BREAST) b. ___ (OVARY)
B95.	Did she ever have any other kind of cancer?	[ ] Yes (B96) [ ] No (NEXT SISTER)	[ ] Yes (B96) [ ] No (NEXT SISTER)	[ ] Yes (B96) [ ] No (B98)
B96.	What kind of cancer did she have?	a. _____ b. _____	a. _____ b. _____	a. _____ b. _____
B97.	How old was she when it was diagnosed?	a. _____ b. _____ (NEXT SISTER)	a. _____ b. _____ (NEXT SISTER)	a. _____ b. _____

B98. Altogether, how many brothers or half-brothers did your father ever have? ___ (B99)
[ ] None (C1)

		Oldest Brother	2nd Brother	3rd Brother
B99.	Is his (oldest, 2nd, etc.) brother still living?	[ ] Yes (B100) [ ] No (B101)	[ ] Yes (B100) [ ] No (B101)	[ ] Yes (B100) [ ] No (B101)
B100.	How old is he?	_____ (B102)	_____ (B102)	_____ (B102)
B101.	How old was he when he died?	_____	_____	_____
B102.	Is he your father's full brother, a half brother or an adopted brother?	[ ] Full brother [ ] Half brother (mother's side) [ ] Half brother (father's side) [ ] Adopted (NEXT BROTHER)	[ ] Full brother [ ] Half brother (mother's side) [ ] Half brother (father's side) [ ] Adopted (NEXT BROTHER)	[ ] Full brother [ ] Half brother (mother's side) [ ] Half brother (father's side) [ ] Adopted (B106)
B103.	Did he ever have any kind of cancer?	[ ] Yes (B104) [ ] No (NEXT BROTHER) [ ] Don't Know (NEXT BROTHER)	[ ] Yes (B104) [ ] No (NEXT BROTHER) [ ] Don't Know (NEXT BROTHER)	[ ] Yes (B104) [ ] No (B106) [ ] Don'tKnow(B106)
B104.	What kind of cancer did he have?	a. _____ b. _____	a. _____ b. _____	a. _____ b. _____
B105.	How old was he when it was diagnosed?	a. _____ b. _____ (NEXT BROTHER)	a. _____ b. _____ (NEXT BROTHER)	a. _____ b. _____

B106. Was your father or his brothers or sisters twins?

[ ] Yes (specify:_____)
[ ] No

(IF MORE THAN 10 MINUTES HAS ELAPSED:)

These are all the questions that I have on your family's history. The rest of the questions will take about 15 minutes.

B107. Would you like to continue now, or would you like to take a break?

[ ] Yes, break
[ ] No, continue

C. PREGNANCY AND FERTILITY

Now I am going to ask you questions about your health. First, I would like to ask you about pregnancies you may have had, including any miscarriages, stillbirths, or induced abortions.

C1. Have you ever been pregnant?

[ ] Yes (C2)
[ ] No (C23)

C2. How many times, in total, have you been pregnant? (PROBE: Include live births, stillbirths, miscarriages, and induced abortions.)

#___ ___

C3. How many liveborn children have you had?

#___ ___

C4. Have you had any:		C5. How many?
a) Miscarriages?	[ ] Yes (C5) [ ] No	_____
b) Stillbirths?	[ ] Yes (C5) [ ] No	_____
c) Induced abortions?	[ ] Yes (C5) [ ] No	_____

Now I would like to ask some specific questions about your pregnancies.

		1st preg	2nd preg	3rd preg	4th preg
C6.	What was the result of your (1st/2nd/etc.) pregnancy? (PROBE: Was it a liveborn, stillborn, miscarriage, or induced abortion?)	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know	Livebirth Stillbirth Miscarriage Abortion Multiple Preg now Don't know
C7.	How many weeks or months did the pregnancy last?	__ __ wks OR __ __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know	__ __ wks OR __ __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know	__ __ wks OR __ __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know	__ __ wks OR __ __ mos "Full term" NOS "Early" NOS "Late" NOS Don't know
C8.	In what month and year did this pregnancy end?	_ _/_ _	_ _/_ _	_ _/_ _	_ _/_ _
	LIVEBORN ONLY:				
C9.	Was it a boy or a girl?	Boy Girl Twin girls Twin boys Twin girl, boy	Boy Girl Twin girls Twin boys Twin girl, boy	Boy Girl Twin girls Twin boys Twin girl, boy	Boy Girl Twin girls Twin boys Twin girl, boy
	LIVEBORN ONLY:				
C10.	What was the baby's birthweight?	_ _/_ _ lbs oz	_ _/_ _ lbs oz	_ _/_ _ lbs oz	_ _/_ _ lbs oz
	LIVEBORN ONLY:				
C11.	Did you breastfeed this(these) child(ren) for 2 weeks or longer?	Yes No (NEXT PREG)	Yes No (NEXT PREG)	Yes No (NEXT PREG)	Yes No (C13)
C12.	How long did you breastfeed this child?	__ __ wks __ __ mos __ __ yrs Still nursing (NEXT PREG)	__ __ wks __ __ mos __ __ yrs Still nursing (NEXT PREG)	__ __ wks __ __ mos __ __ yrs Still nursing (NEXT PREG)	__ __ wks __ __ mos __ __ yrs Still nursing

C13. Have any of your children ever had cancer?

[ ] Yes (C14)
[ ] No (C17)

C14. Which child was this? (USE NUMBER FROM CHART)	C15. What kind of cancer did s/he have?	C16. How old was s/he when it was diagnosed?
___ ___ (PROBE FOR ANY OTHER CHILDREN)	_____	_____
___ ___	_____	_____

C17. Did you ever take medication to prevent a miscarriage or to "hold" a pregnancy?

[ ] Yes (C18)
[ ] No (C23)
[ ] Don't know (C23)

	1st	2nd	3rd
C18. Which pregnancy was this? [REFER TO CHART - C6]	_____	_____	_____
C19. What was the name of the medication?	_____ Don't know, pills Don't know, shots	_____ Don't know, pills Don't know, shots	_____ Don't know, pills Don't know, shots
C20. How many weeks pregnant were you when you started taking it?	__ __ wks __ __ mos "Early" NOS "Late" NOS Don't know	__ __ wks __ __ mos "Early" NOS "Late" NOS Don't know	__ __ wks __ __ mos "Early" NOS "Late" NOS Don't know
C21. How many weeks or months during this pregnancy did you take it?	__ __ wks __ __ mos Don't know	__ __ wks __ __ mos Don't know	__ __ wks __ __ mos Don't know
C22. Did you take medication to prevent miscarriage or to hold a pregnancy another time?	Yes (C18/2nd) No (C23)	Yes (C18/3rd) No (C23)	Yes No

C23. Was there ever a time in your life when you tried for at least 12 months to become pregnant without being able to?

[ ] Yes (C24)
[ ] No (C26)

C24. Did you or your husband or partner ever have tests done for fertility?

[ ] Yes (C25)
[ ] No (C26)

C25. Did the doctor say the problem was due to you, your husband or partner, or both of you?

[ ] Self
[ ] Husband/partner
[ ] Both
[ ] No problem
[ ] Doctor didn't know
[ ] Don't know

C26. Have you ever taken fertility drugs, such as Clomid or Perganol, to stimulate ovulation?

[ ] Yes (C27)
[ ] No (C31)

	1st	2nd
C27. What was the name of the medication?	_____ Don't know, pills Don't know, shots	_____ Don't know, pills Don't know, shots
C28. In what month and year did you start taking it?	__ __/__ __	__ __/__ __
C29. For how many months did you take it?	_____	_____
C30. Did you take fertility drugs after that?	[ ] Yes (C27/2nd) [ ] No (C31)	[ ] Yes [ ] No

C31. Have you ever taken birth control pills to either regulate your period or for birth control?

[ ] Yes (C32)
[ ] No (C36)

	1st PILL USE	2nd PILL USE	3rd PILL USE
C32. In what month and year did you (first/next) begin to use them?	__ __/__ __ Don't know	__ __/__ __ Don't know	__ __/__ __ Don't know
C33. What was the name of the pill you used?	_____ Don't know	_____ Don't know	_____ Don't know
C34. How long did you take them continuously this time?	__ __ mos __ __ yrs Less than 1 month Don't know	__ __ mos __ __ yrs Less than 1 month Don't know	__ __ mos __ __ yrs Less than 1 month Don't know
C35. Did you take birth control pills after that?	Yes (NEXT USE) No (C37)	Yes (NEXT USE) No (C37)	Yes No

C36. What was the <u>main</u> reason you never used birth control pills?
(CHECK ALL THAT APPLY)
[ ] Doctor recommended against
[ ] Respondent concerned about family history
[ ] Respondent concerned about general safety
[ ] Personal choice, or no need

C37. Are there any other hormone medications that you ever took for any reason, other than those we have already discussed?

[ ] Yes (C38)
[ ] No (D1)

C38. What was the name of the medication?

_____
[ ] Don't know

C39. For what reason were you taking this medication?

_____

C40. In what month and year did you start taking it?

__ __/__ __

C41. For how many months did you take it?

_____

D. MEDICAL HISTORY

Now I would like to ask you some more questions about your health.

D1. Did a doctor ever tell you that you had any of the following conditions:		D2. How old were you when you were first told you had this?
a) Gallstones or gallbladder disease	[ ] Yes [ ] No	_____
b) Severe acne	[ ] Yes [ ] No	_____
c) Diabetes (not during a pregnancy)	[ ] Yes [ ] No	_____
d) Colon polyps (PROBE: polyps in the colon)	[ ] Yes [ ] No	_____
e) Excess body and facial hair (hirsutism)	[ ] Yes [ ] No	_____
f) Ovarian cyst	[ ] Yes [ ] No	_____
g) High blood pressure (not during a pregnancy)	[ ] Yes [ ] No	_____
h) High cholesterol	[ ] Yes [ ] No	_____

Now I would like to ask you about surgical procedures you may have had before this year.

D2. Did you ever have any surgery to remove any part of your ovaries or uterus?

[ ] Yes (D3)
[ ] No (D5)

D3. How old were you when you had this surgery?

__ __
Age

D4. After this surgery, did you take any estrogens such as Premarin?

[ ] Yes
[ ] No

Now I'd like to ask you some questions about things that may have happened before you were found to have breast cancer.

D5. Did a doctor ever tell you that you had fibrocystic breast disease?

[ ] Yes (D6)
[ ] No (D7)

D6. How old were you the first time you were told this?

__ __
Age

D7. Before (1 YEAR PRIOR TO REFERENCE DATE), did you ever have a breast biopsy or aspiration?

[ ] Yes (D8)
[ ] No (D11)

D8. What was the reason for the breast biopsy or aspiration?

_____

D9. In what year was this done?

_____

D10. What was found?

_____

D11. Before (1 YEAR PRIOR TO REFERENCE DATE), did you ever have any surgery that changed the size or shape of your breasts?

[ ] Yes (D12)
[ ] No (D15)

D12. Was this surgery to increase the size, or was it to reduce the size or shape?

[ ] Increase
[ ] Reduce

D13. How old were you when you had this surgery?

__ __
Age

D14. Which procedure was used? (PROBE)

[ ] MASTECTOMY DUE TO CANCER
[ ] PROPHYLACTIC MASTECTOMY
[ ] BIOPSY/LUMPECTOMY
[ ] BREAST PROSTHESIS INSERTED (AUGMENTATION)
[ ] COSMETIC REDUCTION
[ ] OTHER _____

Now I would like to ask you a few questions about when you were diagnosed with breast cancer.

D15. In what month and year were you first told that you had breast cancer?

__/__
(month) (year)

D16. Was your cancer first diagnosed in your left, right, or both breasts?

[ ] LEFT ONLY
[ ] RIGHT ONLY
[ ] BOTH
[ ] DON'T KNOW

D17. How was your breast cancer first discovered: did you first notice a problem, was it found during a routine mammogram, or did you doctor notice a problem?

[ ] SELF-DETECTED
[ ] MAMMOGRAPHY-DETECTED
[ ] PHYSICIAN-DETECTED
[ ] OTHER: _____
[ ] DON'T KNOW

D18. Is this the first time that you have had cancer?

[ ] Yes (E1)
[ ] No (D19)

D19. In what organ was your first cancer or tumor diagnosed?

_____

(PROBE: What kind of cancer was it?)
(IF SKIN, PROBE FOR TYPE OF SKIN CANCER)

D20. How old were you when this first cancer (NAME OF CANCER) was diagnosed?

__
Age

E. SMOKING

E1. Have you smoked at least 100 cigarettes, that is, 5 packs or more, in your entire life?

[ ] Yes (E2)
[ ] No (F1)

E2. How old were you when you started smoking cigarettes?

__ __
Age

E3. Do you smoke cigarettes now?

[ ] Yes (E5)
[ ] No (E4)

E4. How old were you when you stopped smoking cigarettes?

__ __
Age

E5. During the years you were smoking regularly, how many cigarettes did you usually smoke per day?

_____
OF CIGARETTES/DAY

F. HEIGHT, WEIGHT, VITAMIN USE

Now I have some questions that have to do with the time when you were a young teenager, say around 12 years of age or around the 7th grade.

F1. **How old were you when you had your first menstrual period?**

__ __ years old
[ ] Never started
[ ] Don't know

F2. **When you were that age, how did your height compare with other girls your age? Were you: shorter, somewhat shorter, about the same, somewhat taller, or much taller?**

[ ] MUCH SHORTER
[ ] SOMEWHAT SHORTER
[ ] ABOUT THE SAME
[ ] SOMEWHAT TALLER
[ ] MUCH TALLER

F3. **And when you were that age, how did your weight compare with other girls your age? Were you: much thinner, somewhat thinner, about the same, somewhat heavier, or much heavier?**

[ ] MUCH THINNER
[ ] SOMEWHAT THINNER
[ ] ABOUT THE SAME
[ ] SOMEWHAT HEAVIER
[ ] MUCH HEAVIER

F4. **At what age did your menstrual periods become regular; that is, you could usually predict about when they would start?**

__ __ years old
[ ] Never became regular
[ ] Don't know

F5. **Did your periods become regular naturally, or did they become regular because of taking birth control pills?**

[ ] Naturally
[ ] Birth control pills
[ ] Some other way

Now I have a few questions about physical activities when you were around 12 years old. I'd like you to think about 2 different levels of physical activity: vigorous activities, and more moderate activities.

F6. Around this age, did you participate in vigorous physical activities like running, basketball, lap swimming, field hockey, dance, or gymnastics?

[ ] Yes (F7)
[ ] No (F9)

F7. How often did you participate in vigorous physical activities when you were 12?

__ __ per _____
times day/week/month/year
[ ] Don't know

F8. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

F9. Did you participate in moderate physical activities like recreational volleyball, softball, brisk walking, or leisurely biking when you were 12?

[ ] Yes (F10)
[ ] No (F12)

F10. How often did you participate in moderate physical activities when you were 12?

__ __ per _____
times day/week/month/year
[ ] Don't know

F11. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

Now let's talk about when you were (in your early 20's/around 20 years old).

F12. How would you describe what your body build was at that age: would you say that you were very slender, about average, a little overweight, or very overweight? (PROBE: Do not include time that you were pregnant.)

[ ] VERY SLENDER
[ ] ABOUT AVERAGE
[ ] A LITTLE OVERWEIGHT
[ ] VERY OVERWEIGHT
[ ] DON'T KNOW

F13. Approximately how tall were you at that age?

__/__ __
ft inches
[ ] Don't know

F14. Approximately how much did you weigh at that age?

__ __ __ pounds

Now I have a few questions about physical activities when you were around 20 years old. Again, I'd like you to think about 2 different levels of physical activity: vigorous activities, and more moderate activities.

F15. Around this age, did you participate in vigorous physical activities like running, basketball, lap swimming, or gymnastics?

[ ] Yes (F16)
[ ] No (F18)

F16. How often did you participate in vigorous physical activities when you were 20?

__ __ per _____
times day/week/month/year
[ ] Don't know

F17. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

F18. Did you participate in moderate physical activities like recreational volleyball, softball, brisk walking, or leisurely biking when you were 20?

[ ] Yes (F19)
[ ] No (F21)

F19. How often did you participate in moderate physical activities when you were 20?

__ __ per _____
times day/week/month/year
[ ] Don't know

F20. Were you required to keep your weight low in order to participate in these activities?

[ ] Yes
[ ] No
[ ] Don't know

(IF AGE 20, GO TO G1)

Now I have some questions about your weight since you were 20 years old.

F21. What has been your lowest weight since age 20, not counting this past year?

___
lbs
[ ] Don't know

F22. How old were you when you first weighed that?

__ __ yrs old
[ ] Don't know

F23. What is the most that you ever weighed? (PROBE: Do not include any times you were pregnant or nursing.)

___
lbs
[ ] Don't know

F24. How old were you when you first weighed this?

__ __ yrs old
[ ] Don't know

F25. When you gain weight, where on your body do you tend to gain it most easily: below the waist, around and above the waist, or above and below the waist equally? (PROBE: Do not include time when you were pregnant.)

[ ] BELOW THE WAIST
[ ] AROUND AND ABOVE THE WAIST
[ ] ABOVE AND BELOW WAIST EQUALLY
[ ] NEVER CARRIED EXTRA WEIGHT

G. ALCOHOL USE

The next set of questions is related to beverages that you may have consumed. First, I'd like you to think about when you were in your teens (PROBE: age 16 to 17).

G1. When you were in your teens, that is, around age 16 or 17, was there ever a period where you drank beer, wine, or liquor at least once a week?

[ ] Yes (G2)
[ ] No (G8)

G2. Did you drink beer at least once a week when you were in your teens?

[ ] Yes (G3)
[ ] No (G4)

G3. When you drank beer in your teens, how many beers on average did you drink in a week?

_____
[ ] Don't know

G4. Did you drink wine at least once a week when you were in your teens?

[ ] Yes (G5)
[ ] No (G6)

G5. When you drank wine in your teens, how many glasses on average did you drink in a week?

_____ of _____
glasses/bottle
[ ] Don't know

G6. Did you have drinks containing liquor at least once a week when you were in your teens? (PROBE: Liquor includes things like vodka, whiskey, gin, and brandy.)

[ ] Yes (G7)
[ ] No (G8)

G7. When you had drinks containing liquor in your teens, how many drinks or shots on average did you have in a week?

_____ of _____
drinks/shots/bottle
[ ] Don't know

Now I would like you to think about when you were (in your early 20's/around 20).

G8. When you were (in your early 20's/around 20), was there ever a period when you drank beer, wine, or liquor at least once a week?

[ ] Yes (G9)
[ ] No (H1)

G9. Did you drink beer at least once a week when you were (in your early 20's/around 20)?

[ ] Yes (G10)
[ ] No (G11)

G10. When you drank beer (in your early 20's/around 20), how many beers on average did you drink in a week?

_____
[ ] Don't know

G11. Did you drink wine at least once a week when you were (in your early 20's/around 20)?

[ ] Yes (G12)
[ ] No (G13)

G12. When you drank wine (in your early 20's/around 20), how many glasses on average did you drink in a week?

_____ of _____
glasses/bottle
[ ] Don't know

G13. Did you have liquor drinks at least once a week when you were (in your early 20's/around 20)?

[ ] Yes (G14)
[ ] No (H1)

G14. When you had liquor drinks (in your early 20's/around 20), how many drinks or shots on average did you have in a week?

_____ of _____
drinks/shots/bottle
[ ] Don't know

H. PRENATAL INFORMATION

(IF RESPONDENT IS ADOPTED, GO TO SECTION I.)

Now, I would like to ask you questions about when your mother was pregnant with you. Perhaps your mother has told you about some of her experiences or things that happened when she was pregnant with you. Please answer to the best of your knowledge.

H1. Did your mother take DES while she was pregnant with you? DES is a medicine that was sometimes used to hold onto a pregnancy.

[ ] Yes
[ ] No
[ ] Don't know

H2. Did a doctor ever tell your mother that she had diabetes during her pregnancy with you?

[ ] Yes (H3)
[ ] No (H4)
[ ] Don't know (H4)

H3. Did your mother have diabetes when she was younger, that is, before any of her pregnancies?

[ ] Yes
[ ] No
[ ] Don't know

H4. Were you born prematurely? (PROBE: Before 36 weeks)

[ ] Yes
[ ] No
[ ] Don't know

H5. How much did you weigh when you were born?

__ __/__ __
lbs oz
[ ] Don't know

H6. Was this a twin pregnancy?

[ ] Yes
[ ] No

H7. When you were born, did you have any problems or conditions, such as a birth defect?

[ ] Yes (H8)
[ ] No (H9)
[ ] Don't know (H9)

H8. What kind of problem or birth defect did you have when you were born?

_____

H9. Did your mother breastfeed you?

[ ] Yes (H10)
[ ] No (H11)
[ ] Don't know (H11)

H10. Did your mother breastfeed you: less than 3 months, between 3 months and 9 months, or more than 9 months?

[ ] LESS THAN 3 MONTHS
[ ] 3 - 9 MONTHS
[ ] MORE THAN 9 MONTHS
[ ] DON'T KNOW

H11. To the best of your knowledge, when your mother was pregnant with you, did she smoke?

[ ] Yes
[ ] No
[ ] Don't know

H12. When your mother was pregnant with you, did your father smoke?

[ ] Yes
[ ] No
[ ] Don't know

H13. When you were a child, did either of your parents smoke at home?

[ ] Yes
[ ] No
[ ] Don't know

I. OCCUPATION; END

Those are all my questions about your health and your family. My final questions are about jobs that you may have ever had as an adult.

I1. Have you ever been employed outside the home?

[ ] Yes (I2)
[ ] No (I6)

I2. When you were employed outside the home, what was your usual occupation? (PROBE: That is, what was your complete job title?)

_____

I3. How old were you when you first began working as a (JOB TITLE)?

__ __ years old

I4. Have you ever worked in the field of medical radiation, or ever trained to work in it?

[ ] Yes (I5)
[ ] No (I6)

I5. How old were you when you began working or training in it?

__ __ years old

I6. My last question now is: Have you ever used an electric blanket, or an electric mattress pad, on a regular basis?

[ ] Yes (I7)
[ ] No (I8)

I7. How old were you when you began using it on a regular basis?

__ __
Age

(END OF INTERVIEW)

I8. Thank you very much for your help in our survey. Your answers will be very helpful in our research. May we contact you again if we need additional information?

[ ] Yes (I9)
[ ] No (I10)

I9. Could you provide me with the name, address, and phone number of someone who will always know where to get in touch with you?

_____ NAME
_____ ADDRESS
_____ PHONE

I10. I would like to arrange to collect a blood sample from you. We can do this in one of two ways; one is to send a blood collection kit to you for you to take to your next doctor's appointment. The second way is to arrange to have a nurse come to your home. Which do you prefer?

[ ] Send kit to patient
[ ] Nurse to come to home

(IF THE KIT IS SENT TO THE PARTICIPANT) The blood draw should be free, but if it is not, please forward the bill to me.

(FOR ALL PARTICIPANTS) In the blood collection kit, there will be three consent forms for you to sign. One will be the study consent. Please sign it in the presence of someone else/the nurse; this person will witness your signature. The second consent is a medical records and paraffin block release; this is so we can look at your records when you were treated for breast cancer and so that we can get a sample of your tumor. The third consent is an optional consent which will allow us to use a tube of blood for future studies. You will not have to have an extra tube of blood drawn, but you can refuse to sign this consent.

Please send the consents back to us in the pre-addressed envelope, separate from the blood. There is a letter explaining all of this to you in the kit.

I11. If you have any other questions, please call me at _____. My name again is (YOUR NAME). Thank you again for your time.

END CALL AND RECORD RESULT CODE AND TIME ENDED ON QUESTIONNAIRE COVER

APPENDIX 4:

Consent Forms

DANA-FARBER CANCER INSTITUTE

INFORMED CONSENT FOR RESEARCH

Issue Date: 1/31/95 #94-161

PROTOCOL NUMBER & TITLE: Biological Specimen Bank to Enhance Population-Based Studies of Inherited Cancer Genes

SUBJECT/PATIENT NAME: _____ DFCI I.D. NUMBER: _____

BIOLOGICAL SPECIMEN BANK TO ENHANCE POPULATION-BASED STUDIES OF INHERITED CANCER GENES

Breast cancer is the most common cancer in women. Approximately 180,000 women will have been diagnosed with breast cancer in 1992. Of these, an estimated 10,000 cases are due in part to an inherited breast cancer susceptibility gene. It is estimated that approximately 5% of breast cancers occur in women who have an inherited susceptibility to the disease. However, the frequency of inherited susceptibility to breast cancer is approximately 25% in women who develop breast cancer before age 36.

Inherited traits are carried in genes. Genes come in pairs: two copies of each gene are found in almost every cell in the body. They are arranged on structures called chromosomes, and contain the hereditary information that determines many different characteristics. Genes often contain small changes or alterations. Sometimes these changes do not cause any problems, but some changes are more serious and can interfere with the way the gene is supposed to work. This research focuses on genes whose functions are thought to be important to the way cells usually work. Changing only one gene of the pair can cause a dramatic increase in a person's susceptibility to cancer development. Because cancer has occurred in you at an unusually early age, we are interested in looking for a possible genetic predisposition to cancer. This will be done by looking for alterations in genes in your blood.

Presently, our main research goal is to establish a resource for laboratory scientists nationwide to examine blood and tumor specimens of young women to obtain preliminary data on how frequently alterations in certain genes might play a role in breast cancer development. These laboratory investigators will not know your identity and will not be able to contact you directly. Their studies include the recently discovered breast cancer gene called BRCA1 (BReast CAncer 1), and other genes that might be discovered in the future. Another goal is to examine possible relationships between environmental exposures and genetic susceptibility to breast cancer.

The discovery of the breast cancer gene BRCA1 and other cancer susceptibility genes is new. Researchers are still studying ways to improve our ability to identify and understand genetic changes in people who develop cancer. We will answer any question you may have regarding genetic susceptibility to cancer based on your personal medical history and/or family history.

Because any early laboratory results might be wrong, we will not be releasing any laboratory test results of our analysis to you or to your doctor. This current work is in the realm of research, and any results should be regarded as preliminary findings and not definitive. However, we hope that the research will produce new knowledge that will yield definitive results in the future. If you feel that it would be too difficult for you not to know the results, even though the scientific significance of the result may be unknown, you may decide to not participate.

Initials of Participant/Date _____ Initials of Witness/Date _____

DANA-FARBER CANCER INSTITUTE

INFORMED CONSENT FOR RESEARCH

Issue Date: 1/31/95 #94-161

PROTOCOL NUMBER & TITLE: Biological Specimen Bank to Enhance Population-Based Studies of Inherited Cancer Genes

SUBJECT/PATIENT NAME: _____ DFCI I.D. NUMBER: _____

We can notify you when a commercial or clinical test for BRCA1 is available from any source. A commercial or clinical test will provide more definitive results on DNA analysis of the breast cancer gene. In addition, it is possible that a commercial or clinical test for BRCA1 may be available before this study is completed. You should not feel any obligation one way or another to have the BRCA1 test. If you choose to have this test done, it will not change your participation in this research study.

To participate in this study, you will be asked to provide approximately 50 cc of blood (10 teaspoonsful) for use in efforts to develop new information and promising genetic technologies by multiple researchers in the United States.

You will be asked to designate one tube of blood for storage and possible future genetic studies by the Principal Investigators. This is optional and does not require drawing an additional tube of blood. You will be asked to sign a second consent form if you decide to do this. If, in the future, specific findings are documented in you from this tube of blood, you will be offered the opportunity to learn the results of the research. Disclosure of results will occur in separate studies; clinical intervention, including genetic counseling, will be available. You may decline to participate in such additional studies; results will remain confidential.

We will also ask you to complete a questionnaire - by mail and over the telephone or at the time of your blood draw. The questionnaire should take about 15 to 20 minutes to complete. The questions are about your family's history of cancer, your own risk factors for breast cancer, and your own cancer history. You may decline to answer any question in the questionnaire. We will ask permission to review your medical record to assist only in our research on breast cancer. We will also ask permission to obtain your stored tumor specimen for molecular analysis. Laboratory researchers who will study your blood and/or tumor specimen will not know the identity of the respondent to the questionnaire.

Risks: There is no risk from the participation in the study, except for the possibility of anxiety from blood drawing and bruising at the blood-drawing site. The amount of blood lost is not clinically important. You are authorized all necessary medical care for injury or illness which is the proximate result of your participation in this research. There is no compensation available for your participation in this research study; however, you understand this is not a waiver or release of your legal rights.

Benefits: There will be no direct benefit to you from participation in this study at this time.

Initials of Participant/Date

Initials of Witness/Date

DANA-FARBER CANCER INSTITUTE

INFORMED CONSENT FOR RESEARCH

Issue Date: 1/31/95 #94-161

PROTOCOL NUMBER & TITLE: Biological Specimen Bank to Enhance Population-Based Studies of Inherited Cancer Genes

SUBJECT/PATIENT NAME: _____ DFCI I.D. NUMBER: _____

Confidentiality: All information obtained in this study will be kept confidential. Your blood specimen will be assigned a code number and your name removed. Your questionnaire will also receive a number, and after it is completed, your name will be removed. The list of names and matching code numbers will be stored separately from the other study information, and will be available only to the study supervisors. This information will not be made available to anyone else, including other participating laboratory investigators, you, or your physician.

Confidential information contained in your medical record may not be furnished to anyone unaffiliated with Dana-Farber Cancer Institute without your written consent, except as required by law or regulation. There is a possibility that your medical record, including identifying information, may be inspected and/or photocopied by the Food and Drug Administration or other Federal or state government agencies in the ordinary course of carrying out their governmental functions. If your record is used or disseminated for government purposes, it will be done under conditions that protect the privacy of the individual to the fullest extent possible consistent with laws relating to the public disclosure of information and the law enforcement responsibilities of the agency.

Use of Specimens: Any tissue or blood obtained for the purposes of this study becomes the property of the Dana-Farber Cancer Institute and the U.S. Government. DFCI may retain, preserve or dispose of these specimens and may use them anonymously to learn about cancer causation and development. Occasionally, laboratory research on human tissue does result in discoveries that become the basis for new research products or diagnostic and therapeutic agents. You understand that your blood sample which you are providing under this study might also be used in other research studies and could potentially have some commercial applicability. Your signature on this consent means that you agree to make a gift to the Institute of any rights to the proceeds from any commercial developments made with, or through the use of, these specimens.

Withdrawal from Study: Once you have signed this consent, you may still withdraw from this study. If you do so, we will not contact you further and we will not communicate the results of any analysis except in the context of research publications; you will not be identifiable.

There are no costs to you for participation in this research study. In the event that at any point in the duration of this study you have any questions about research subjects' rights or research related injuries, or if you feel that you have not been adequately informed of the risks and benefits, or feel under excessive pressure to continue this study against your wishes, a representative of the Human Protection Committee of Dana-Farber is available to speak with you (617-632-3029).

_____ Initials of Participant/Date

_____ Initials of Witness/Date

DANA-FARBER CANCER INSTITUTE

INFORMED CONSENT FOR RESEARCH

Issue Date: 1/31/95 #94-161

PROTOCOL NUMBER & TITLE: Biological Specimen Bank to Enhance Population-Based Studies of Inherited Cancer Genes

SUBJECT/PATIENT NAME: _____ DFCI I.D. NUMBER: _____

If you have any questions regarding this study or cancer genetics or susceptibility, do not hesitate to contact any of the following individuals:

Dr. Frederick Li Principal Investigator (Massachusetts and Connecticut)	(617)632-2508
Dr. Elizabeth Claus Co-Principal Investigator (Connecticut)	(203)785-2838
Jennifer Morgan Study Manager	(617)632-5189 (800)828-6622

Initials of Participant/Date

Initials of Witness/Date

DANA-FARBER CANCER INSTITUTE

INFORMED CONSENT FOR RESEARCH

Issue Date: 1/31/95 #94-161

PROTOCOL NUMBER & TITLE: Biological Specimen Bank to Enhance Population-Based Studies of Inherited Cancer Genes

SUBJECT/PATIENT NAME: _____ DFCI I.D. NUMBER: _____

I have fully explained to the Participant _____ the nature and purpose of the study described above and such risks as are involved in its performance.

_____ Date

_____ Physician's Signature

_____ Physician's Name (Please Print)

I have been fully informed as the procedures to be followed and have been given a description of the attendant discomforts, risks, and benefits to be expected, and the appropriate alternate procedures. In signing this consent form, I agree to participation in this study and I understand that I am free to withdraw my consent at any time, without prejudice of any kind. I understand also, that if I have any questions at any time, they will be answered.

I have been given a copy of this consent form.

_____ Signature of Witness

_____ Signature of Participant

_____ Printed Name of Witness

Please complete the following (please print):

Your name: _____

Permanent Address: _____

_____

_____

Do you wish to be notified when a commercial or clinical test becomes available for the breast cancer susceptibility gene, BRCA1?

( ) yes ( ) no

May we contact you to offer potential participation in future studies of breast cancer causation?

( ) yes ( ) no

FORM 2540-1 REV. 1-93

DANA-FARBER CANCER INSTITUTE

INFORMED CONSENT
FOR RESEARCH

Issue Date: 1/31/95 #94-161

PROTOCOL NUMBER & TITLE: Biological Specimen Bank to Enhance Population-Based Studies of Inherited Cancer Genes

SUBJECT/PATIENT NAME: _____ DFCI I.D. NUMBER: _____

BIOLOGICAL SPECIMEN BANK TO ENHANCE POPULATION-BASED STUDIES OF INHERITED CANCER GENES

OPTIONAL

CONSENT FOR FUTURE USES OF BLOOD SAMPLES

I, _____, designate one tube of blood to be used for storage and possible future uses by the Principal Investigators, Frederick Li, MD and his associates. I understand that if, in the future, specific findings about the development of breast cancer are documented in me from this tube of blood, I will be offered the opportunity to learn the results of the research. I may, however, choose not to learn the results at that time. I voluntarily and freely donate any and all blood product samples to the Dana-Farber Cancer Institute and the U.S. Government and hereby relinquish all right, title, and interest to said items.

_____ _____

Date Signature of Participant

_____

Signature of Witness

DANA-FARBER
CANCER INSTITUTE

THE JIMMY FUND

44 Binney Street, Boston, MA 02115

DIVISION OF CANCER EPIDEMIOLOGY AND CONTROL
Tel. 617-632-3158
Fax 617-632-3161

EARLY BREAST CANCER STUDY

For the purposes of medical research, I give Frederick P. Li, MD, or his appointed representative permission to review my medical records and paraffin blocks (tumor specimen).

Patient's Name «fname» «lname» Signature _____

Patient's Birth Date «dob» Today's Date _____

Names of Hospital(s), Physician(s), Dates, Records Departments:

_____

_____

_____

_____

_____

APPENDIX 5:

Letter from Brigham and Women's Hospital Pathology Department

Harvard Medical School

Brigham and Women's Hospital

Janina A. Longtine, M.D.
Assistant Professor of Pathology

Associate Director of Surgical Pathology
Department of Pathology
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115
(617) 732-7444
FAX: (617) 264-6330
jalongtine@bics.bwh.harvard.edu

October 16, 1996

Ms. Jennifer Morgan
Dana Farber Cancer Institute
44 Binney Street, Mayer 31.31
Boston, MA 02115

Dear Ms. Morgan:

Enclosed are 10 unstained, unheated sections of breast tissue from [redacted] breast biopsy performed on [redacted] ([redacted]). The tissue contains an area with the carcinoma and an area of normal breast.

As we briefly discussed, due to the current economic environment, the department has instituted a charge for recuts of tissue blocks for research purposes. This is to cover the administrative costs of organizing the materials, reviewing the slides to select an apporpriate block and the technical costs of preparing the slides. The charge is $25.00 for the first slide and $5.00 for each additional unstained slide. The charges will be waived in this initial case.

Please contact me if you have any questions.

Sincerely,

Janina Longtine, M.D.